HEART REVIEW

Natriuretic peptides in heart valve disease

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Synthesis and release of B-type natriuretic peptide (BNP) are increased in heart failure, and plasma concentrations provide important therapeutic and prognostic information. Recent studies have shown that BNP concentrations are also increased with disease of the mitral and aortic valves. The extent of the increase is broadly related to the severity of the valve abnormality and the degree of consequent cardiac remodelling. BNP concentrations appear to relate to prognosis in these patients and might have a role in identifying suitable candidates for cardiac surgery. This paper reviews the current literature and identifies areas where further research is required if assessment of BNP is to be of practical use.

The natriuretic peptides, particularly B-type natriuretic peptide (BNP), have an emerging role in the diagnosis, treatment, and prognostic assessment of patients with heart failure.[1] Important differences in the physiology of the natriuretic peptides underlie their potential clinical use. Atrial natriuretic peptide (ANP) is stored in granules within the atria and released rapidly in response to atrial stretch.[2] BNP, on the other hand, is stored in only limited amounts and increased secretion relies on increased synthesis consequent on activation of the BNP gene.[3] BNP is produced as a prohormone that is cleaved in the circulation into active BNP and the N-terminal peptide NT-proBNP.[3] Both can be assayed but NT-proBNP has a longer plasma half life and higher plasma concentrations.[1] In the normal heart the atria are the main source of BNP, but where ventricular wall stress is chronically increased ventricular BNP production is upregulated, which becomes predominant.[3] Ventricular dysfunction increases plasma concentrations of both ANP and BNP but the relative increase in BNP is the greater.[2]

Current management strategies for patients with valve disease rely heavily on the presence or absence of symptoms and the echocardiographic assessment of left ventricular (LV) and valve function.[4] These assessments are not always straightforward. The onset of symptoms in patients with valve disease is often insidious and, particularly in less active patients, may not be readily apparent. Organic mitral regurgitation is a good example. Severe mitral regurgitation makes the LV look dynamic on two dimensional echocardiography and may thus mask an early deterioration in pump function. Despite recent recommendations,[5] few cardiologists formally quantify the severity of mitral regurgitation and most simply eyeball ejection fraction. By the time symptoms are obvious or ejection fraction has clearly deteriorated, LV impairment will be irreversible. Similar concerns apply in aortic valve disease. A biomarker that reflects the severity of valve disease and the development of early ventricular dysfunction would be of great interest. Since BNP production is increased in response to increased myocardial wall stress it may potentially fulfil this role.

Natriuretic peptides in aortic valve disease

Some studies have found that natriuretic peptides correlate with the severity of aortic stenosis, expressed either as transvalvar gradient or valve area.[6–12] These peptides also correlate with LV afterload expressed as end systolic wall stress, with the degree of LV hypertrophy, a consequence of increased afterload, and negatively with LV ejection fraction.[6 10–14] Correlations are generally closer with BNP and NT-proBNP than with ANP.

Gerber *et al*[10] from New Zealand studied patients with aortic stenosis and a transvalvar gradient of at least 25 mm Hg. Log transformed concentrations of natriuretic peptides (BNP, NT-proBNP, and ANP) correlated extensively with measures of the severity of stenosis and measures of LV chamber size, wall thickness and stress, ejection fraction, left atrial size, and right ventricular pressures. Overall natriuretic peptide concentrations increased steadily with decreasing valve area and increased greatly when ejection fraction fell below 50%. The closest relations were seen for NT-proBNP. Of 74 patients, 45 (61%) were symptomatic with breathlessness, angina, or (pre)syncope. As expected, symptomatic patients were older, had smaller valve areas, and had higher concentrations of all three peptides. However, the relation between log transformed peptide concentrations and symptoms persisted after correction for ejection fraction, valve area, age, sex, and renal function. NT-proBNP was the best discriminator for symptoms with an area under the receiver operator characteristic curve of 0.84 with a cut off of 60 pmol/l. Interestingly, peptide concentrations correlated with breathlessness but not with angina or (pre)syncope. Why this should be the case is not clear, as chest pain in patients with aortic stenosis and normal coronary arteries is known to be related to wall stress. However, pathological breathlessness is difficult to define and in practice symptoms of breathlessness and chest discomfort are not clearly demarcated. Lim

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Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

et al[15] obtained similar results with 70 patients with severe aortic stenosis (aortic valve area < 1 cm^2). In their study a BNP concentration of 66 pg/ml identified symptoms with an area under the receiver operator characteristic curve of 0.86.

The results of these studies are striking, as at face value natriuretic peptide concentrations apparently can discriminate between New York Heart Association (NYHA) classes I and II. Attractive as it is, this concept is not supported by the largest study so far published. Bergler-Klein *et al*[16] studied 130 patients with severe aortic stenosis defined by a peak transvalvar velocity of > 4/ms or valve area < 1 cm^2. Eighty seven patients were symptomatic at study entry. In contrast to the results of Gerber *et al*[10] and Lim *et al*[15], concentrations of natriuretic peptides (in this case without log transformation) did not distinguish between patients in NYHA classes I and II, but there were significant differences between classes II and III and between class III and class III–IV.

Although BNP may not discriminate effectively between asymptomatic and mildly symptomatic patients with aortic stenosis, there is some evidence that BNP can identify the transition from compensated hypertrophy to early decompensation in patients with preserved ejection fraction. In an elegant study Vanderheyden and colleagues looked at a relatively homogeneous group of 40 patients with symptomatic aortic stenosis, a transvalvar velocity of at least 2.5 m/s, and normal ejection fraction.[14] Patients were subdivided on the basis of an LV end diastolic pressure of 16 mm Hg into one group with intact and one with impaired preload reserve. Patients with an LV end diastolic pressure $>$ 16 mm Hg had similar valve areas and LV mass index but greater end systolic and end diastolic wall stress, larger end diastolic volumes, lower ejection fractions, and afterload mismatch. Qi *et al*[7] reported similar results in a group of patients subdivided by an LV end diastolic pressure of 12 mm Hg.[9] Patients in the study of Vanderheyden *et al*[12] with intact preload reserve had substantially higher BNP concentrations than normal controls but those with raised filling pressure had a further increase. Unlike in earlier studies BNP and systolic wall stress were not correlated but BNP did correlate with measures of diastolic wall stress and LV mass. The relation with diastolic stress is in keeping with experimental observations in which diastolic stretch induces BNP gene expression.[17] Qi *et al* studied both ANP and BNP.[9] Whereas BNP related better to indices of aortic stenosis and LV remodelling, ANP correlated more closely with atrial pressure. This observation raises the possibility that simultaneous measurement of both peptides can provide complementary information with the rise of ANP indicating a rise in preload.

All patients in the study of Vanderheyden *et al*[12] were already symptomatic and thus had an established indication for surgery.[4] However, 50% of them had developed symptoms despite no evidence of haemodynamic decompensation. It is not clear from the paper how many patients developed breathlessness as opposed to exertional (pre)syncope or angina but, as discussed above, the difference may be important.[15 16] Control of BNP synthesis and release in aortic stenosis seem likely to result from a complex interplay between systolic load, ventricular hypertrophy, and diastolic stretch. Plasma concentrations are increased in asymptomatic patients with moderate or severe stenosis and increase further with the onset of breathlessness and further still with the onset of haemodynamic decompensation.

A striking result of the study of Bergler-Klein *et al*[16] was the relation of baseline peptide concentrations to the development of symptoms during follow up. Of the 43 patients who were asymptomatic at baseline, 14 developed symptoms during follow up; in this group, baseline peptide concentrations, especially N-terminal BNP, were substantially higher than in those who remained asymptomatic throughout. The difference was most notable in six patients who developed acute congestive heart failure. Interestingly patients who developed angina but not breathlessness had low N-terminal BNP concentrations both at baseline and at follow up. By multivariate analysis only N-terminal BNP and LV ejection fraction were independent predictors of remaining symptom free. Gerber *et al*[18] obtained similar results in a group of 29 initially asymptomatic patients followed up with serial BNP concentrations for 18 months. Patients with a baseline NT-proBNP above normal (> 50 pmol/l) were much more likely (about 10 times) to develop symptoms. However, a high NT-proBNP concentration lacked specificity, as only around half of those with increased concentrations at baseline actually became symptomatic within the period of observation.

Natriuretic peptides appear to discriminate well for a successful postoperative outcome in patients undergoing aortic valve replacement. In the series of Bergler-Klein *et al* N-terminal BNP was the only independent predictor of survival and of good symptomatic status and along with preoperative ejection fraction was an independent predictor of postoperative LV ejection fraction.[16] These findings were broadly confirmed by both Lim *et al*[15] and Vanderheyden *et al*.[12]

There are variable changes in ANP and BNP in the immediate aftermath of aortic valve replacement surgery but long term follow up data are scarce.[14 19] Qi *et al*[14] found a decrease in ANP concentrations at four and 12 months postoperatively, most notably in those patients with an increased preoperative pulmonary wedge pressure. In contrast BNP concentrations remained more or less unchanged, possibly because LV hypertrophy did not regress during follow up. There are no data on whether late regression of ventricular hypertrophy is associated with downregulation of BNP production.

The New Zealand group has published a small study of natriuretic peptides in aortic regurgitation.[20] In 40 patients with moderate to severe aortic regurgitation concentrations of all three peptides were higher in the 27 asymptomatic patients than in matched controls and higher again in 13 symptomatic patients. Ten of the 13 symptomatic patients were in NYHA class II. Both asymptomatic and symptomatic patients had substantially dilated LVs with a mean end diastolic diameter of 6.6 and 6.9 cm, respectively. Symptomatic patients had slightly lower ejection fractions (54% *v* 58%) and slightly greater end systolic wall stress, but other echocardiographic parameters were very similar. This study is too small to draw any clinically useful conclusions but it is interesting that log transformed concentrations of all three peptides were considerably lower than in equivalent patients with aortic stenosis despite substantial LV dilatation and, by implication, increased diastolic wall stress.[10] Another small study of 12 asymptomatic patients with aortic regurgitation and preserved LV function found a correlation between BNP and the extent of ventricular remodelling.[21]

Natriuretic peptides in mitral valve disease

A few small studies have examined natriuretic peptide concentrations in mitral stenosis.[22–24] Plasma concentrations of both ANP and BNP are increased and decline with successful balloon valvotomy. There are more published data on natriuretic peptides in patients with mitral regurgitation. Several early studies found increased peptide concentrations in patients with mitral regurgitation but none of these distinguished patients with ischaemic regurgitation from those with non-ischaemic regurgitation.[25–27] In a population based study of elderly people living in Finland, N-terminal ANP was significantly increased in those with moderate or severe mitral regurgitation.[25] A study of patients with

suspected LV dysfunction also found an association between NT-proBNP and the severity of mitral regurgitation.[26] Another small study found increased plasma BNP concentrations in patients with moderate or severe mitral regurgitation of mixed aetiology.[27] None of these studies excluded or satisfactorily controlled for patients with angina pectoris, LV dysfunction secondary to myocardial infarction, or concomitant valve disease, and all used qualitative methods for assessing mitral regurgitation.

More recently Sutton *et al*[28] studied 49 patients with varying degrees of isolated mitral regurgitation due to degenerative or rheumatic disease and an ejection fraction of > 55%. Concentrations of ANP, BNP, and NT-proBNP were increased as compared with controls. Of all the peptides NT-proBNP correlated most closely with clinical and echocardiographic variables and was related to the severity of mitral regurgitation and left atrial dimension as well as age and sex. There was no relation with LV dimensions or ejection fraction but this may reflect the relatively narrow range of LV function and the use of dimensions rather than volumes to assess LV size.

By far the largest study yet published is that of Detaint *et al*[29] from the Mayo Clinic, who followed up a relatively unselected group of 124 patients with more than mild organic mitral regurgitation. Just over a third of their patients had severe mitral regurgitation. These authors found that symptoms, the presence of atrial fibrillation, and the extent of both atrial and ventricular remodelling were independently associated with higher BNP concentrations. The severity of mitral regurgitation, although univariately associated with BNP concentrations, was not an independent predictor. Uniquely, this study also examined outcome over a mean of 4.4 years. After age, sex, functional status, LV function, and severity of regurgitation were controlled for, BNP was independently predictive both of death and the combined end point of heart failure or death. The implication of these findings is that BNP is not just a marker for the severity of mitral regurgitation or a surrogate for symptoms. Rather it seems to reflect the consequences of mitral regurgitation for the heart, including adverse clinical outcome.

Potential clinical use and limitations

The test of whether BNP is clinically useful in valve disease is whether it simplifies patient management and ultimately contributes to improved outcomes. In symptomatic patients with an established indication for operation a high BNP concentration predicts a worse late outcome and may be useful in risk stratification.[16 28] Withholding surgery is, however, not justified on the basis of a high BNP.

If BNP is to have a specific role in valve disease it is likely to be in the optimal management of those patients with asymptomatic severe aortic stenosis or degenerative mitral regurgitation who do not fit standard indications for surgery. An increased BNP in these patients can in principle be used to select patients at high risk of developing symptoms or ventricular impairment over a relatively short time frame and prompt earlier operation. Similarly, BNP may also be useful in assessing those patients with non-specific symptoms, such as fatigue, not clearly related to the valve disease where a high concentration may also prompt early surgical referral. The relation between BNP and exercise testing needs to be further investigated. In apparently asymptomatic patients with aortic stenosis the development of symptoms during exercise testing is a strong predictor of the development of spontaneous symptoms and the need for valve replacement.[30] BNP may possibly provide additional predictive information but no data are yet available.

Concentrations of natriuretic peptides are influenced by factors other than valve disease. Plasma BNP is increased by, among other conditions, coronary disease, atrial fibrillation, and renal failure. Patients with aortic stenosis often have aortic regurgitation or mitral regurgitation. Mild regurgitation is unlikely to influence BNP concentrations to any great extent but moderate or worse insufficiency will have an impact. The presence of potential confounding factors is not unique to natriuretic peptides but it does raise questions about the wider applicability of BNP measurement in patients with valve disease. Studies performed to date have generally selected patient populations with ''pure'' valve disease free of most confounding variables and have been relatively small, cross sectional, or both. Larger longitudinal studies of a broader range of asymptomatic patients with aortic valve disease and degenerative mitral regurgitation are needed to define better the relation between BNP concentrations and the onset of symptoms or the first signs of LV dysfunction.

CONCLUSIONS

Numerous studies have looked at the relation of natriuretic peptides to the severity of valvar heart disease. In general, peptide concentrations are greater with increasingly severe valve abnormality, with the presence of symptoms, and with pronounced ventricular remodelling. Both in aortic stenosis and in degenerative mitral regurgitation there is evidence that BNP can identify those asymptomatic patients on the verge of developing symptoms or haemodynamic compromise. Larger scale longitudinal studies are required to determine whether BNP can have a clinically useful role.

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IMAGES IN CARDIOLOGY

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Swing-like movement of pigtail catheter in a patient with ruptured chordae tendinae

A 77-year-old woman was admitted to our hospital with congestive heart failure. A pansystolic murmur was audible at the apex. Echocardiography revealed a flail anterior leaflet of the mitral valve with massive mitral regurgitation, indicating a diagnosis of mitral regurgitation caused by rupture of the chordae tendinae. The left atrial dimension was 53 mm, the left ventricular end diastolic dimension was 56 mm, and the left ventricular ejection fraction was 85%. Medical treatment was administered and then right- and left-sided cardiac catheterisation was performed. Pulmonary capillary wedge pressure was 25 mm Hg, and the cardiac index was 1.87 l/min/m^2. The panels show that a pigtail catheter inserted into the left ventricle swung between the left ventricle and the left atrium (to view video footage visit the *Heart* website—http://www.heartjnl.com/supplemental). Coronary arteriography revealed intact coronary arteries. The patient underwent mitral valve replacement without any complications. This unique finding that has not been previously reported is thought to be caused by flailed mitral valve with severe mitral regurgitation.

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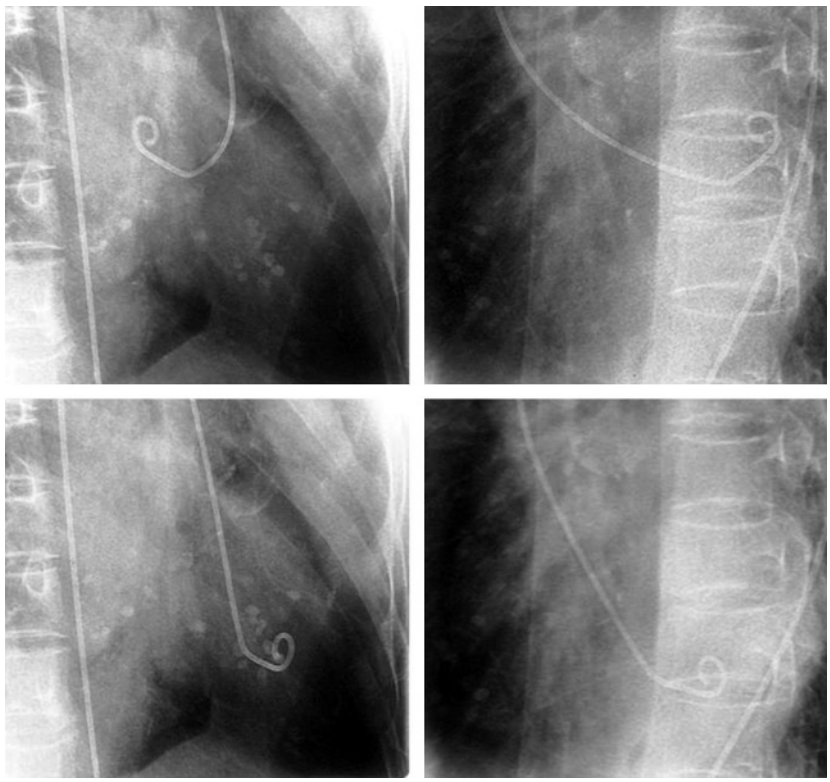
To view video footage visit the *Heart* website—http://www.heartjnl.com/supplemental



Right (left panels) and left (right panels) anterior oblique projections show that the pigtail catheter swung between the left ventricle and left atrium during the cardiac circle (upper panels = systolic phase, lower panels = diastolic phase).